Behavioural Brain Research 286 (2015) 285–292

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

A mild traumatic brain injury (mTBI) induces secondary attention-deficit hyperactivity disorder-like symptomology in young rats

Richelle Mychasiuk*, Harleen Hehar, Michael J. Esser

Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB T2N 1N4, Canada

HIGHLIGHTS

- Mild brain injuries induce lingering symptomology in at least 15% of children.
- Young rats with an early mTBI/concussion develop deficits of sustained attention.
- The injury is also associated with impulsivity and impaired response inhibition.
- Animals with an mTBI were not necessarily hyperactive.
- In the response inhibition measurement males were more impaired than females.

ARTICLE INFO

Article history:
Received 9 December 2014
Received in revised form 16 January 2015
Accepted 4 March 2015
Available online 11 March 2015

Keywords:
Go/No-Go
Executive function
Impulsive
Secondary ADHD
Weight-drop

ABSTRACT

Although attention-deficit hyperactivity disorder (ADHD) is commonly reported after moderate and severe traumatic brain injury (TBI), research is struggling to find a strong link between mild TBI or concussion and ADHD. Epidemiological studies often generate conflicting results which may be related to the difficulty identifying the lingering symptoms of mTBI, the lack of baseline knowledge and the possible exacerbation of pre-existing ADHD symptomology, and/or differential diagnostic criteria for secondary ADHD. The purpose of this study was to determine if a mild TBI/concussion in the juvenile period (postnatal day 30) could induce ADHD-like symptoms in young rodents. Using the Go/No-Go paradigm of the 5-choice serial reaction task, sustained attention, impulsivity, and response inhibition was measured. The open field was also used to measure activity levels at two time points. Animals that experienced an mTBI in the juvenile period exhibited ADHD symptomology, with sex-differences present on one of the tasks. Significant deficits were identified in sustained attention, response inhibition, and impulsivity. Immediately after the mTBI, all rats were hypoactive in the open field, and while male animals exhibited a trend toward hyperactivity in the long-term, females continued to trend toward hypoactivity for the duration of the experiment. These findings provide a unique platform upon which preventative and therapeutic strategies can be implemented and tested in an effort to improve ADHD-like symptoms following mTBI.

1. Introduction

Traumatic brain injury, generally resulting from neonatal trauma, automobile accidents, or falls, is the leading cause of disability and mortality in children and adolescents [1]. Mild traumatic brain injury (mTBI) or concussions are the most common form of neurological insult in this age group, accounting for ~80–90% of all brain injuries [2]. mTBIs generally do not produce structural damage to the brain, but are instead characterized by the rotational acceleration or deceleration forces imparted on the brain that lead to microscopic damage and the neurological impairment that follows [3]. Although many children experience only transient symptomology that resolves without medical intervention, a significant proportion suffers from lingering and progressive pathologies that interfere with normal daily activities, such as school attendance [4]. The developmental trajectory and maturational status of the brain at the time of insult is an especially important factor affecting the pathophysiology and resultant dysfunction following pediatric mTBI [1]. For instance, the juvenile period extending into late adolescence, represents an important time for maturation of

* Corresponding author at: Alberta Children's Hospital Research Institute, University of Calgary, Room 274, Heritage Medical Research Building, 3330 Hospital Drive N.W., Calgary, AB T2N 1N4, Canada. Tel.: +1 403 210 7178; fax: +1 403 955 7649.
E-mail address: rmmychas@ucalgary.ca (R. Mychasiuk).

http://dx.doi.org/10.1016/j.bbr.2015.03.010
0166-4328/

the prefrontal cortex and the development of executive function and social skills [5]. Many of the most commonly reported symptoms by children and adolescents who have experienced an mTBI are related to the complex processes associated with cognition and executive function. Studies often show that individuals with mTBI demonstrate decreased concentration, difficulties paying attention and remembering, and slowed reaction times [6–8]. These findings are consistent with parent and caregiver reports who indicate attention and memory problems, impatience, and impulsivity, in their children following an mTBI [9]. As this is a critical window for prefrontal cortex maturation, experiencing an mTBI during this time period may increase an individual's risk for disorders of cognitive control and executive function.

Attention-deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders identified in children and adolescents, with approximately 10% of school-aged children receiving a diagnosis of primary or secondary ADHD (s-ADHD) [10]. ADHD is a behavioral disorder characterized by abnormal levels of impulsivity, hyperactivity, and inattention [11]. A plethora of literature has demonstrated an increased prevalence of acquired or secondary ADHD-like symptomology following a moderate or severe brain injury [12], with s-ADHD being the most common psychiatric disorder in children with TBI [13]. Following the injury, these children and adolescents exhibit reduced inhibitory control, increased hyperactivity, poor sustained and divided attention, in addition to memory problems [9,14–17]. A more extensive examination of the symptomology demonstrated that divided and sustained attention appear to be most vulnerable to brain injury in children, whereas attention span and response flexibility seem to be more resistant [15,18]. ADHD is therefore not a homogenous disorder, but rather an umbrella construct that encompasses multiple overlapping but dissociable cognitive profiles [19]. This is an important concept for two reasons. First, it shows that just as brain injuries differ substantially, the ADHD symptomology resulting from these injuries will also be heterogeneous; it is not an all or nothing phenomena. Second, it helps explain why the literature regarding mild TBI and s-ADHD is ambiguous.

The majority of literature has shown that moderate and severe TBI are significant risk factors for ADHD, however there is no convincing evidence for the role that mild TBI may play in inducing s-ADHD (e.g. [17,20,21]). Studies typically report conflicting results with respect to ADHD following mTBI. Some human studies have found that mTBI does not increase an individual's risk for an ADHD diagnosis [22], whereas other studies show a strong relationship between mTBI and poor inhibitory control/impulsivity [15,16]. These discrepancies may be associated with different characterizations of mild injuries and injury pathophysiology, or the result of differential outcome reporting, with some studies requiring medically diagnosed ADHD and others examining individual aspects of the disorder, such as hyperactivity. The purpose of this study was to examine whether or not characteristic traits often associated with ADHD could be induced in juvenile rats following an mTBI/concussion. As there is a great deal of heterogeneity in the prevalence and symptom presentation of males and females with respect to mTBI and ADHD, juvenile rats from both sexes were used in the study. Following the mTBI or sham injury at postnatal day 30 (P30), the 5-choice serial reaction task (Go/No-Go paradigm) and open field were used to measure hyperactivity, sustained attention, impulsivity, and response inhibition. In addition, because prior literature has demonstrated that social cognition, social dynamics, and peer-to-peer play are affected by TBI [23–26], all of which involve executive function of the prefrontal cortex [27]; this experiment sought to determine if manipulation of the social environment could influence mTBI induced deficits of executive functions involved in ADHD, specifically attention, impulsivity, and response inhibition.

2. Materials and methods

2.1. Subjects and mTBI procedure

All experiments were carried out in accordance with the Canadian Council of Animal Care and approved by the University of Calgary Conjoint Faculties Research Ethics Approval Board. Forty-eight (24 male:24 female) in-house bred Sprague Dawley rats were caged in same-sex groups of 4 in a temperature controlled husbandry room (21 °C). The husbandry room was maintained on a 12:12 light:dark cycle (lights on at 0700) and animals had *ad libitum* access to food and water. When pups reached postnatal day 30 (P30), half received an mTBI using the modified weight drop technique as previously described [28], and the other half received a sham injury. Briefly, animals were lightly anesthetized and placed chest down on a scored piece of tinfoil that was suspended 10 cm above a foam sponge. A 150 g weight was dropped through a guide tube from a height of 0.5 m, at which point the weight produced a glancing impact to a closed-head, propelling the rat through the tinfoil. The rat landed on the collection sponge in the supine position after undergoing a 180° vertical rotation that induces acceleration/deceleration and rotational forces on the brain. Immediately after injury induction, topical lidocaine was applied to the rat's head and it was placed in a clean, warm cage to recover. Animals experiencing a sham injury were exposed to the same preparation procedure (lightly anesthetized), were quickly placed on the scored tinfoil, removed from the tinfoil, also received administration of topical lidocaine and were then placed in a clean, warm cage to recover.

2.2. Validating the presence of an mTBI

The research assistants administered two tests to validate the presence of an mTBI/concussion, (a) time-to-right (immediately post-injury) and (b) beam-walking (24 h post-injury). Prior research has demonstrated that specific performances on these 2 tasks (increased time-to-right and increased hind-leg foot-slips) are associated with post-concussion symptomology and the presence of a mild injury [28].

2.2.1. Time-to-right

Immediately after the mTBI or sham injury, animals are placed in a clean warm cage to recover in the supine position. The time required for each animal to right itself from the supine position to a prone or standing position is recorded as the time-to-right.

2.2.2. Beam-walking

Twenty-four hours post-injury, animals are tested in a beam walking paradigm similar to that described by Schallert et al. [29]. Animals traversed a 165 cm tapered beam from a wider starting position to the narrower end at their home-cage. The beam is equipped with 2 cm wide 'safety' ledges that catch the rat's foot when it slips while negotiating the narrowing walk. The rat is provided with a single learning trial which is followed by 4 videotaped trials, each separated by 60 s rest periods. The video camera is set up at the starting point and positioned to view the entire length of the beam. A researcher blind to the experimental conditions scored the videos for the number of hind-leg foot slips each rat experiences during the 4 test trials.

2.3. Hyperactivity

Animals were tested in the Open Field paradigm on P32 and P58 to measure average locomotor activity. On each of these days, rats were placed in the center of a circular open field (diameter 100 cm) and allowed to explore the environment for 5 min. An overhead